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Structure determination of antimicrobial peptides in model membranes and live bacteria

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Resistance to antibiotics is a growing health concern worldwide. Antimicrobial peptides (AMPs) present an alternative to conventional antibiotics but details of their mechanism of action and the basis for differences in their potency observed between different bacterial strains remain unclear. Structural information is crucial for defining the molecular mechanism by which these peptides recognize and interact with a particular lipid membrane. Nuclear magnetic resonance (NMR) structural investigations of cationic AMPs from Australian tree frogs in a range of different lipid systems will be discussed. Although these AMPs are unstructured in aqueous solution, they are alpha-helical in hydrophobic or membrane-like environments. The degree of helicity depends on membrane curvature and surface charge with a greater helical stretch in phospholipid bilayer membranes compared to micelles. Molecular dynamics simulations of the AMP, maculatin 1.1, show N-terminal exposure to the solvent and indicated that the peptide bends to adapt to the micelle curvature. Maculatin induced greater headgroup and acyl-chain perturbations for anionic phospholipids, which are found in bacterial membranes. The AMP appeared to lie on the surface of charged lipid membranes but insert in a transmembrane fashion with zwitterionic bilayer membranes. Solid-state NMR and dynamic nuclear polarization (DNP) studies of maculatin in live bacteria also support a transmembrane orientation. DNP NMR using spin-labelled peptides in combination with specifically 13C and 15N labelled maculatin give insight into pore formation and how AMPs self-assemble within bacterial membranes. The results of these structural studies could be used to design more potent AMPs for therapeutic applications.

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